REMARKS

Claims 10-19 had been canceled, without prejudice, in light of the final election/restriction requirement. Claim 20 has been deleted, without prejudice.

A terminal disclaimer is hereby provided to address the provisional double patenting rejection.

Nothwithstanding Applicants' traversal of the rejection over JP 01011141, in the effort to progress this patent application to issuance without delay, **claim 1** has been amended by incorporating the subject matter of **claim 2** which has not been rejected over JP 01011141, without prejudice. Claim 2 has been canceled without prejudice.

Claim 1 has been further amended to specify that the open cell lattice is formed from an oil-in-water emulsion, deleting reference to water dispersible porous bodies, and specifying that hydrophobic materials are contained in the lattice. Support for this subject matter may be found in the Specification at page 2, paras. 1 and 2; page 4, last para.; page 5, Para. 2 and 3, and page 9, last paragraph.

Claim 1 has been further amended to specify that hydrophobic material incorporated into the polymeric lattice has two types of pores as described. Support for this subject matter may be found in the Specification at page 4, bottom para.; page 5, paras. 2 and 3; and page 11, bottom para.

Claim 3 has been amended to delete reference to vinyl pyridine. Claim 4 has been amended to deleted selected materials and to specify the sodium salt of carboxymethylcellullose (SCMS).

Claim 7 has been amended to be consistent with claim 1. Claim 9 has been amended to depend on claim 1.

Claim 21 has been amended, without prejudice, to refer to dispersions only and to clarify that said dispersions are in fact solutions of water soluble polymeric material and surfactant having a dispersed hydrophobic material therein.

Care has been taken not to introduce any new matter.

The Claims Are Not Obvious

A series of obviousness rejections have been made based on JP01-011141 (Fujimoto *et al.*), US6451348B1 (Jeong *et al.*), US4371516 (Gregory *et al.*), US5648093 (Gole *et al.*) and US5502082 (Unger *et al.*). Applicants respectfully traverse.

JP01-011141 (Fujimoto et al.)

The Examiner objects that claims 1 and 3-5 are obvious over Fujimoto *et al.* in paragraphs 7 and 8 of the Action. A formal translation into English of Fujimoto *et al.* is enclosed for reference.

From the translation, it is clear that Fujimoto *et al.* is quite different from amended claim 1 for a number of reasons. Firstly, Fujimoto *et al.* discloses use of a ***hydrophilic*** (but not water soluble) polymer; its uses are described on page 2 as cigarette filters, filters, wound coverings, packing materials, haemostatic products, pharmaceutical product carriers, feminine hygiene products and artificial bait, all of which are possible because of the material's water-absorbing characteristics, adsorption characteristics, flexibility and elasticity. These applications would prove to be a nonsense if the material in Fujimoto *et al.* where to dissolve or disperse on contact with an aqueous medium!

Secondly, it is clear from Fujimoto *et al* that the product formed has ***two-dimensional*** ordering of pores, rather than three-dimensional as is claimed; the pores are formed by ice crystals which grow upwardly through the thickness of the polymeric material to form elongate, cylinder-like pores. This is confirmed in the Examples section in Fujimoto *et al.*.

Thirdly, the process for forming the material is not oil-in-water emulsion-templating (as is discussed in amended claim 1); the method described in Fujimoto *et al.* involves making an aqueous solution or suspension of the hydrophilic polymer in water, adding surfactant to the solution, pouring the resultant solution into a tray and

freeze-drying. There is no suggestion of making an emulsion, or of freeze-drying the emulsion to remove the solvent from each phase of the emulsion.

Fourthly, there is no disclosure in Fujimoto *et al.* of including a water-insoluble material within the material that is formed by freeze-drying, unlike the present invention.

Thus the claims of the present invention are believed to be non-obvious over Fujimoto *et al.*.

US6451348B1 (Jeong et al.)

Claims 1-3, 5-8 and 20-21 were rejected as obvious over Jeong *et al.* in paragraphs 9 to 13 of the Action.

This document discloses a polymeric matrix-type drug delivery system for the controlled release of drugs. The matrix is formed from a water-in-oil emulsion (in which the drug is dissolved in the aqueous phase and the polymer is dissolved in the oil phase), which is shaped into a "desired matrix shape" (e.g. by casting as a film onto a plate), allowed to air-dry until the matrix has hardened and then vacuum-dried to remove residual aqueous and non-aqueous solvents.

Firstly, it is important to note that Jeong *et al.* is directed to a drug-delivery system ***for the controlled release of drugs***, which according to column 1, lines 23-29 means that a drug is released from the polymeric matrix according to a time schedule. Immediately this teaches that the polymeric matrix does not simply dissolve or otherwise break-down within the human or animal body upon introduction therein, because this would defeat the object of the drugs being controllably released. However, the polymeric matrix may biodegrade over a longer period of time, once its useful drug-release life has ended.

Secondly, it is stated that the drugs to be incorporated into the polymeric matrix are "osmotically active, water-soluble drugs" that are released into the human or animal

body by "an induced osmotic pressure across a pseudo-semi-permeable polymer matrix", such that:

(1) the drug is released at a constant rate;

(2) the drug is released at a controlled rate; and

(3) very little drug is ultimately left as a residue in the polymeric matrix

- see column 3, lines 11-22.

There is no disclosure is Jeong *et al.* of porous bodies in the form of powders, beads (but not spherical beads having an average bead diameter of 0.2 to 5 mm) or moulded bodies comprising a three-dimensional water-soluble polymeric/surfactant lattice in which a water-insoluble material is incorporated. The present invention enables the preparation of aqueous dispersions of otherwise water-insoluble materials, by rapid dissolution of the porous bodies and consequent dispersion of the water-insoluble materials. Therefore, the amended claims are not obvious over Jeong *et al.*

US4371516 (Gregory et al.)

The Examiner objects that claims 1-3, 5-8 and 20-21 are obvious over Gregory *et al.* in paragraphs 14 to 20 of the Action.

This document discloses a pharmaceutical (or other chemical) dosage form that is rapidly disintegrable. This is achieved by providing a "shaped" article comprising an open matrix network of water-soluble or water-dispersible polymeric carrier material carrying a chemical – see column 1, lines 21-24, 34-36, 44-49, 54-57 and 58-64. It is said that the open matrix network is similar in structure to a solid foam (column 2, lines 48-49) and that rapid disintegration of said matrix results in the rapid release of any pharmaceutical or other chemical carried by the matrix (column 2, lines 58-60).

The dosage form is prepared by freeze-drying a ***single-phase*** composition (not an oil-in water emulsion) comprising the chemical and a solution of the carrier material in solvent, and optionally other ingredients such as a surfactant (column 3, line 57 to column 4, line 7). Thus there is no disclosure in Gregory *et al.* of porous bodies as

claimed in amended claim 1, and especially of such porous bodies having two different types of pores therein.

US5648093 (Gole et al.) and US5502082 (Unger et al.)

The Examiner has objected that claims 1-9 and 20-21 are obvious over Gregory *et al.* in view of Gole *et al.*, Unger *et al.* and Fujimoto *et al.*, the arguments being provided in paragraphs 21 to 29 of the Action.

She also objects that claims 1-7 and 20-21 are obvious over Unger *et al.* in paragraphs 30 to 34 of the Action, and that claims 1-9 and 20-21 are objected to as being obvious over Unger *et al* in view of Gole *et al* in paragraphs 35 to 39 of the Action.

Gole *et al.* is directed to a method of preparation of a solid dosage form comprising a porous network of matrix material that is able to disperse rapidly (in less than 10 seconds) in water – see column 1, lines 20-22 and column 2, lines 42-45. The matrix material may be a polymer (see column 5, lines 53-64) and it may be used along with a surfactant (see column 6, lines 8-17). The resultant dosage form may exhibit "high uniform porosity" – see column 4, lines 24-27).

The dosage form is formed by subjecting a matrix-material solution to lyophilisation ***or*** solid-state dissolution (column 2, lines 54-55), which as is apparent from the description, are quite different techniques.

Column 2, line 64 to column 3, line 6 describe the case where lyophilisation is used: before lyophilisation (which is acknowledged to be a well-known method of freeze-drying in column 1, lines 24-27) is performed, any active agent contained in the dosage form can be coated with a protective coating to protect the active agent from process solvents, etc. Not much more is said about lyophilisation in Gole *et al.* other than in Examples 36, 37 (refers to 36), 38 (refers to 36), 40, 41, 42 and 43, all of which described the formation of a single-phase solution which is transferred to a mould and

subsequently subjected to lyophilisation to produce a network of matrix material that rapidly dissolves when taken orally. This is quite obviously different from the product defined in amended claim 1.

Column 3, line 46 to column 4, line 16 describe the case where solid-state dissolution (SSD) is used: a matrix-forming agent is dissolved or dispersed in a ***first solvent***, solidified (by cooling/freezing – see column 8, line 66 to column 9, line 7) and subsequently contacted with a ***second solvent*** which is substantially miscible with the now-solid first solvent, such that the first solvent ***substantially dissolves*** into the second solvent, leaving behind the solid (porous) matrix-forming agent in a first solvent/second solvent liquid. Once removed from the first solvent/second solvent liquid, the porous matrix may be "dried" to remove all traces of solvent.

Column 5, lines 36-52 provide further detail of the SSD process, whilst Examples 1, 2, 3, 4 (refers to 1), 5 (refers to 4), 6 (refers to 1), 7 (refers to 1), 8 (refers to 6), 9 (refers to 1), 10 (refers to 9), 11 (refers to 4), 12 (refers to 1), 13 (refers to 1), 14 (refers to 1), 15 (refers to 1), 16 (refers to 1), 17 (refers to 1), 18, 19, 20, 21, 22 (refers to 19), 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 and 39 describe the formation of a single phase solution from carrier material and a first solvent, transferral of the single phase solution to a mould and cooling with dry ice or freezing in a freezing tunnel to form a solid, and subsequently transferring the solid into a second solvent, whereby the first solvent dissolves into the second solvent leaving a network of carrier material behind. Again the product formed is quite different from the product of the present invention.

Unger *et al.* describes a ***cross-linked*** porous body that is derived from water-soluble, hydrogel polymer. This document is therefore not relevant to the present invention because a cross-linked porous body is not a water-soluble porous body, as is well known in the art. In this respect, to further describe and elucidate the difference between the present invention and the Unger *et al.*, attached is an extract from the textbook "Introduction to Organic Chemistry", 3rd edition, page 1113, authored by Andrew Streitwieser Jr. and Clayton H. Heathcock, which states that:

"Cross-linking has a large effect on physical properties because it restricts the relative mobility of polymer chains. Polystyrene, for example, is soluble in many solvents such as benzene, toluene, and carbon tetrachloride. Even with only 0.1% divinylbenzene, however, the polymer no longer dissolves but only swells"..

A Notice of Allowance is earnestly solicited.

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(54) Title of the invention: Method of manufacturing hydrophilic polymer porous material

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Specification

1. [Title of the invention]

Method of manufacturing hydrophilic polymer porous material

2. [Claims]

1) A method of manufacturing hydrophilic polymer porous material characterised in that, in a method of obtaining a porous material by a freeze-drying method using a hydrophilic polymer aqueous liquid, freeze-drying is performed with addition of a surfactant to this aqueous liquid.

2) The method according to claim 1 characterised in that porous material can be manufactured having any desired pore diameter by suitable selection of the added amount of surfactant in the range 0.1 to 100% with respect to the dry weight of the hydrophilic polymer.

3. [Detailed description of the invention]

Field of industrial application

The present invention relates to a method in which a suitable quantity of surfactant is added to an aqueous solution of a hydrophilic polymer material, an aqueous suspension, or a mixture of these (hereinbelow termed an aqueous liquid) and freeze-dried: in more detail, the present invention relates to a method of manufacturing a porous body wherein the pore diameter of the

polymer porous body product obtained can be adjusted at will by selection of the added amount of this surfactant and having pores wherein the direction of formation of the pores is practically parallel with respect to the thickness direction of the sample.

The porosity obtained according to the present invention is a porosity that provides ample ventilation characteristics, water absorbing characteristics, adsorption characteristics, flexibility, and elasticity, and makes it possible to supply the material for applications such as cigarette filters, filters, wound coverings, packing materials, haemostatic products, pharmaceutical product carriers, feminine hygiene products, or artificial bait etc.

Prior art

The freeze-drying technique is currently used over a wide range in various fields such as food product technology or pharmaceutical product manufacturing: in most cases, the object is to make possible storage for a long period by drying without altering the quality of the original product, or to manufacture products that are capable of being restored to their original condition rapidly in use. In this case, it may be experienced that destruction of cells occurs or non-uniformity is produced on restoration using water, because of the freezing condition, for example the size of the ice crystals, of the water contained, depending on conditions such as the temperature or speed of freezing, or because the growth rate of the ice crystals is slow and uneven.

Also, although the freeze-drying technique for dried bean curd, agar and dried rice cakes etc that has been practised for a long time in Japan is an excellent method for obtaining the aforementioned porous food products, by repeated freezing and drying over a period of time in a comparatively high temperature zone below the freezing point, the pore diameter is extremely large.

Similar situations arise even when such porous bodies are manufactured by the freeze-drying method from hydrophilic polymer aqueous liquids; in particular, when attempting to obtain products wherein the thickness of the porous body is at least 10 mm, the size of the ice crystals may reach from a few cm to a few tens of cm and the direction of ice crystal growth may be uneven: consequently, irregularity occurs in regard to the pore diameter and pore direction of the product, with the result that the product is non-uniform and desirable products from the point of view of ventilation characteristics, water-absorptivity and elasticity etc were not obtained.

Problem that the invention is intended to solve

When drying of an aqueous solution of hydrophilic polymer or a uniform aqueous suspension or a liquid mixture of these is performed by the freeze drying method, the size and shape of the pores of the product obtained are determined by the size and shape of the ice crystals that are produced on freezing: however, if for example the freezing temperature is kept low and rapid freezing is performed using liquid nitrogen, with the object of achieving a high freezing speed, small, uniform ice crystals are produced, resulting in a product

of fairly small uniform pore diameter being obtained when this is freeze-dried. However, with this method, there are restrictions regarding the thickness of the sample. Also, if a supercooled condition is produced by gradual cooling followed by instantaneous freezing, some of the small crystals of the ice crystals that were initially produced are melted by latent heat when crystallisation takes place, with the result that the remaining ice crystals in the recrystallisation stage become somewhat larger. However, since the ice crystals, which grow considerably in this process, are independent crystals, the pores of the dry product are transformed into independent bubbles.

Also, in the case of a polymer aqueous liquid such as a liquid fibre dispersion other than a pure polymer aqueous solution, which is non-uniform on the micro scale, freezing is made difficult due to the aforementioned super-cooling. Also, when a sample, that is to be dried, of thickness 15 mm to 70 mm, is frozen, even though liquid nitrogen or the like is employed as described above, a temperature gradient is produced in the sample, with the result that freezing takes place gradually from the surface: the ice crystals therefore become large and, proceeding further into the inner layers, the direction of growth of the ice becomes chiefly growth in the direction orthogonal to the thickness direction of the sample, resulting in the product obtained by drying being non-uniform.

Means for solving the problem

As a result of repeated studies in regard to the above problems, the present inventors discovered that the pore diameter and pore direction could be made uniform by freeze-drying performed with addition of a surfactant to a hydrophilic polymer aqueous liquid, and thereby achieved the present invention. As hydrophilic polymer materials employed as raw materials in the present invention, there may be employed natural polymer materials such as proteins such as casein, gelatine, collagen, albumin, fibroin, keratin, fibrin, or gluten, and polysaccharides such as cellulose, starch, agar, carrageenan, konjac mannan, sodium alginate, sodium carboxymethyl cellulose, methyl cellulose, cellulose sulphate, chondroitin sulphate, chitin hyaluronate, or chitosan; and synthetic polymer materials such as polyvinyl alcohol, polyacrylate, polyacrylamide, polyglutamic acid, polyethyleneimine, or other anionic, cationic, non-ionic or amphoteric ionic polymer substances. Also, two or more of these polymer materials may be employed in combination.

These polymer materials may be employed as an aqueous solution by dissolving in water, or as an aqueous dispersion by mechanically comminuting and dissolving in water, or as a mixed liquid of both of these. In this specification, the term "aqueous liquid" includes all of the aforementioned conditions.

According to the present invention, the aforementioned hydrophilic polymer aqueous liquids, in a concentration of 0.05 to 50%, preferably 0.1 to 10%, were uniformly dispersed and 0.1 to 100%, preferably 0.5 to 50% of

surfactant with respect to the dried weight of the polymer material was added thereto in each case; the mixture was allowed to flow into a tray such as to produce a sample thickness 5 to 100 mm, preferably 20 to 70 mm; after completely freezing, irrespective of the freezing temperature or rate of freezing, a hydrophilic polymer porous sample having pores that were parallel with the thickness direction of the sample and that were of uniform pore diameter was obtained by performing freeze-drying.

The surfactant may be any of anionic, cationic, non-ionic, or amphoteric: however, it is necessary to choose a surfactant that does not produce a coagulation reaction with the type of polymer material used. Also, the HLB of the surfactant may be any value in the range 1.8 to 40, but, with regard to the hydrophilic character of polymer materials and aqueous suspensions thereof, the HLB value should preferably be 2 to 20.

The added amount of surfactant is important in determining the pore diameter of the porous material. If the added amount is less than 0.5%, in particular less than 0.1%, the beneficial effect of the present invention does not appear. Also, if the added amount is 50% or more, in particular 100% or more, the properties of the polymer porous material itself are adversely affected. In the above range of added amount of surfactant, the larger the added amount, the smaller is the pore diameter and the more uniform the pores become. The advantage is also obtained that by addition of surfactant, cracking of the material on freeze-drying becomes less likely. Also, the pore diameter is affected by the concentration of the polymer aqueous liquid: finer porous bodies of smaller pore diameter are obtained at higher concentrations.

If the concentration of the polymer aqueous liquid is less than 0.05%, the texture becomes too coarse so that when water absorption takes place, the shape cannot be maintained; if the concentration is 50% or more, the viscosity is high, so this is not practical for spreading the liquid on a tray.

The thickness of the sample that is allowed to flow into the tray should be determined with regard to maintaining a balance between the amount of polymer porous material obtained by a single freeze-drying step and the drying time required for freeze-drying: in practice, 20 to 70 mm is satisfactory.

The description will be continued in further detail below with reference to practical examples. However, the present invention is not restricted to these examples.

Practical examples

1) Commercial methyl cellulose of 4000 CPS was dispersed in water and heated; after cooling, it was uniformly dissolved to obtain a solution of 3% concentration. To this solution was added nonionic surfactant of HLB value 8 in the amount of 5% with respect to the dry weight of the methyl cellulose, and the mixture was mixed uniformly and defoamed. This liquid was introduced into a tray in an amount such as to provide a sample thickness of 30 mm and ordinary freezing was performed, followed by drying, using a freeze-drying machine.

When the porous material obtained was examined using a microscope, it was found that long pores had developed in the thickness direction, with a pore diameter of 50 to 100 μm, and that these were uniformly distributed. Also, scarcely any difference was found between the portions close to the freezing surface i.e. the under-surface of the porous material (surface in contact with the tray) and the remote portions i.e. the inner layer or upper layer.

2) A 0.5% aqueous solution of sodium alginate was prepared and cationic surfactant of HLB value 18 was added thereto in an amount of 50% with respect to the dry weight of the sodium alginate, the mixture was mixed uniformly, and defoamed. When freeze-drying was performed by the same method as in practical example 1), porous material was obtained in which long pores of pore diameter 40 to 70 μm were uniformly arranged in the thickness direction.

3) An aqueous solution of 10% concentration was prepared by dispersing gelatine powder in water with an alkaline process and dissolving by heating. Non-ionic surfactant of HLB value 4 was added thereto in an amount of 2% with respect to the dry weight of gelatine, the mixture was mixed uniformly and defoaming was then performed. The liquid obtained was allowed to flow into a tray in an amount such as to produce a sample thickness of 50 mm and ordinary freezing was performed, followed by drying, using a freeze-drying machine.

A porous material was obtained with long pores of pore diameter 50 to 100 μm in the thickness direction: these pores were uniformly distributed.

Agent: patent attorney Kyozo Yuasa

INTRODUCTION TO ORGANIC CHEMISTRY

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$$Y\cdot + CH_2{=}CHCl \longrightarrow Y{-}CH_2CHCl \longrightarrow\longrightarrow \underset{\text{polyvinyl chloride}}{Y(CH_2CHCl)_nZ}$$

Vinyl chloride is manufactured on an enormous scale, primarily for making polyvinyl chloride, PVC. The 1983 production of PVC was 6.07 billion pounds. Vinyl chloride is manufactured mostly by dehydrochlorination of 1,2-dichloroethane (ethylene dichloride). In 1974 the Occupational Safety and Health Administration concluded that vinyl chloride is a human carcinogen and set maximum limits to exposure.

Polyvinyl chloride is an extremely hard resin. In order to alter the physical properties of the polymer, low molecular weight liquids called **plasticizers** are added in the polymer formulation. Bis-2-ethylhexyl phthalate is one of the compounds added to polyvinyl chloride as a plasticizer. The resulting polymer has a tough leathery or rubber-like texture. It is used in plastic squeeze bottles, imitation leather upholstery, pipes, and so on.

Polytetrafluoroethylene or "Teflon" is a perfluoro polymer having great resistance to acids and organic solvents. It is used to coat "nonstick" frying pans and other cooking surfaces.

$$X{-}(CF_2CF_2)_n{-}Y$$
Teflon

Polystyrene is an inexpensive plastic used to manufacture many familiar household items. It is a hard, colorless, somewhat brittle material.

$$\begin{pmatrix} C_6H_5 \cdot \\ | \\ CHCH_2 \end{pmatrix}_n$$

In the simple formulation of polystyrene, the end groups have been omitted. This simplification is common in the symbolism of polymer chemistry. The end groups constitute a minute portion of a high molecular weight polymer, although their character has a significant effect on the properties of the polymers.

The incorporation of divinylbenzene into the polymerization of styrene provides **cross-linking** because the two vinyl groups can participate in two separate chains and produce a three-dimensional network. Cross-linking has a large effect on physical properties because it restricts the relative mobility of polymer chains. Polystyrene, for example, is soluble in many solvents such as benzene, toluene, and carbon tetrachloride. Even with only 0.1% divinylbenzene, however, the polymer no longer dissolves but only *swells*. This property is important in many uses of polystyrene-derived materials. An example is the polymer used for the Merrifield peptide syntheses (page 949). The 1983 production of polystyrene in its various forms, including copolymers, was 5.55 billion pounds.

Acrylonitrile is another important monomer manufactured in large quantity for use in synthetic fibers and polymers; its 1983 production in the United States was 1.07 million tons. It was once prepared industrially by addition of HCN to acetylene.

$$HC{\equiv}CH + HCN \xrightarrow[NH_4Cl]{CuCl} CH_2{=}CHCN$$

CONCLUSION

The examiner is invited to contact the undersigned if there are any questions concerning the case.

Respectfully submitted,

/Ellen Plotkin/

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